Clean Room Certification – Is Your Compounding Environment in Compliance

Don Filibeck, PharmD, MBA, CSP
Jim Wagner
CE Credit in Five Easy Steps!

1. Scan your badge as you enter each session.
2. Carry your Evaluation Packet to every session so you can add session evaluation forms to it.
3. Track your hours on the “Statement of Session Attendance Form” as you go.
4. At your last session, total the hours and sign both pages of your Statement of Session Attendance Form.
   - Keep the PINK copy for your records.
   - Put the YELLOW and WHITE copies in your Evaluation Packet.
   - Make sure a completed Session Evaluation Form is in your Evaluation Packet for each session you attended.
      - Missing one? Extras are in a file near Registration.
5. Complete the General Attendance Evaluation Form located in your Evaluation Packet—and place it back in your envelope.
   - Write your name on the outside of your Evaluation Packet envelope, seal it, and drop it in the box near Registration.
   - Applying for Pharmacy CPE? If you have not yet registered for an NABP e-Profile ID, please visit www.MyCPEmonitor.net to do so before submitting your packet.
   - You must enter your NABP e-Profile ID in order to receive CE credit this year!
Disclosure Slide

James Wagner is a consultant. Conflict of interest was resolved by peer review of slide content.

Don Filibeck declares no conflicts of interest or financial interest in any service or product mentioned in this program.

Clinical trials and off-label/investigational uses will not be discussed during this presentation.
Overview of the Regulatory or Accrediting Body Oversight of a Compounding Pharmacy

Don Filibeck, PharmD, MBA, CSP
Objectives

- State two incidents that have led to regulatory oversight of compounding pharmacies
- State two of the key provisions of HR3204 Drug Quality and Security Act
- Provide an overview of the Boards of Pharmacy and their regulatory oversight
- List two of the accrediting bodies that provide overview of compounding pharmacies
How Did We Get Here
(lest we forget)

• 05/2001 California – *Serratia marcescens* contaminated betamethasone injection
• 09/2002 South Carolina – *Exophiala* contaminated injectable steroids
• 03/2005 Texas – *Serratia marcescens* contaminated mag sulfate injection
• 09/2005 Maryland – Gram Negative rods found in cardioplegia solution
How Did We Get Here
(lest we forget)

• 03/2011 Alabama – *Serratia marcescens* contaminated parenteral nutrition solutions

• 09/2012 Massachusetts – Fungal meningitis contamination of a injectable steroid

• 2013 – Increased FDA Inspections\(^1\)
  – 54 pharmacies / 9 contract testing labs
  – Eighty (80) 483s published on FDA website
  – Any number of voluntary recalls implemented
Regulatory History$^{2,3,4}$

- 1906 Food and Drug Act
- 1938 Food, Drug and Cosmetic Act
- 1962 Kefauver-Harris Amendments
- 1987 Prescription Drug Marketing Act
- 1997 FDAMA
- 2007 Food and Drug Adm Amendments Act
- 2012 FDASIA (Drug Shortages)
Most Recent Regulation\textsuperscript{5}

- 2013 Drug Quality and Security Act
  - Introduced 09/27/13
  - Sponsor: Fred Upton (R-MI6)
  - Cosponsors: 10 (6D, 4R)
  - Passed House: 09/28/13
  - Passed Senate: 11/18/13
  - Signed by President: 11/27/13
HR3204 Drug Quality and Security Act

- Title 1 – Drug Compounding
- Title 2 – Drug Supply Chain Security
HR3204 Drug Quality and Security Act

• Title 1 – Drug Compounding (aka Compounding Quality Act)\(^6\)
  – Reinstated section 503A of the FDC Act\(^7\)
  – New section 503B Outsourcing Facilities
    • New type of compounding entity
    • Optional registration with the FDA
    • Semi-annual reporting and yearly inspections if registered
  – Establishes an FDA Pharmacy Compounding Advisory Committee (PCAC)
FDA Actions\textsuperscript{8}

- FDA Implementation of the CQA
  - Registration
  - Enhanced communication with the states
  - Creation of an advisory committee
  - Inspection and enforcement

- List of registered outsourcing pharmacies: [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm)

- Section 503A draft guidance document\textsuperscript{9}
- Section 503B registration draft guidance document\textsuperscript{10}
- Additional guidance documents on FDA website\textsuperscript{11}
FDA Expectations

• Boards of Pharmacy continue oversight and regulation of the practice of pharmacy, including traditional pharmacy compounding

• Traditional compounding based on
  – Receipt of an individual’s prescription
  – Done by licensed individual
  – Done in limited quantities
  – Done in compliance with the appropriate United States Pharmacopeia (USP) chapters
  – Drugs on the ‘Do Not Compound’ list are not prepared
Boards of Pharmacy Oversight

- Varies across the country
- BOPs contracting with NABP and others to inspect non-resident pharmacies
- For pharmacies that perform sterile compounding, some boards of pharmacy are requiring that this be part of their most recent inspection
- Updates from the states
  - California
  - Virginia
  - Iowa

Source: Clinical IQ http://www.clinicaliq.com/797-state-survey
Accreditation Body Oversight

• The Joint Commission (TJC)$^{13}$
  – LD.04.01.01 The organization complies with law and regulation
  – MM.05.01.07 The organization safely prepared medications
  – EQ.02.01.01 The organization maintains, tests and inspects medical equipment used in the provision of care, treatment and services

• Accreditation Commission for Health Care (ACHC)$^{14,15}$
  – Standard DRX4-14D: Written policies and procedures are established and implemented relating to special education, experience, or certification requirements for pharmacy personnel to prepare compounded sterile preparations.
  – Standard DRX4-14E: Qualified personnel comply with aseptic technique when compounding sterile preparations.
  – Standards DRX7-8A, DRX7-8B, DRX7-8C and DRX7-8D

• Community Health Accreditation Program (CHAP)

• Others$^{16}$
  – The Compliance Team, HFAP, HQAA, URAC, etc.
Other Guidelines / Resources

• Pharmacy Compounding Accreditation Board (PCAB)
  – http://www.pcab.org/

• USP\textsuperscript{17}
  – Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations
  – Chapter <797> Pharmaceutical Compounding – Sterile Preparations
  – Chapters <1160> <1163> <1176>
  – Chapters in Development: Compounding with Hazardous Drugs, Compounding for Clinical Drug Studies
  – USP Pharmacist Pharmacopeia
  – USP Compounding: A Guide for the Compounding Practitioner
  – FAQs: http://www.usp.org/support-home/frequently-asked-questions/compounding
Other Guidelines / Resources

• ISMP\textsuperscript{18}
  – Safety Summit held October 25 -26, 2011
  – Resources: http://search.ismp.org/cgi-bin/hits.pl?in=517791&fh=80&ph=1&tk=p_JEFeLE%20_JEFeLE-%20K%3ApQ%3AvbVebk%20K%3ApQ%3AvbVebk-
    &su=kKQQwHgg__VbPw.upWghuukbg-uPwureIVeW.Abw&qy=cqPgEAlg%20OW%3FKWe%26HA%26z&pd=1

• ASHP\textsuperscript{19}
  – Sterile compounding resource center: http://www.ashp.org/menu/PracticePolicy/ResourceCenters/Compounding
  – Sterile Compounding Summit: http://www.ashp.org/compounding%20summit

• NHIA
  – Sterile compounding resource center: http://www.nhia.org/resource/sterile/
Questions?
References

electronicreadingroom/ucm340853.htm
2. http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm
5. https://www.govtrack.us/congress/bills/113/hr3204
376732.htm#section
376733.htm
m375804.htm
77052.pdf
M377051.pdf
References

13. The Joint Commission: Comprehensive Accreditation Manual for Home Care Effective 01/2014
14. ACHC: 2013 Accreditation Standards for DME/Pharmacy
Certification of Sterile Compounding Facilities

James T Wagner
Controlled Environment Consulting
Learning Objectives

At the end of this session, you will be able to:

• Describe the certification Guide for Sterile Compounding Facilities (CETA CAG-003-2006)
• Describe the term “state of control” related to the certification process for primary and secondary engineering controls
• Relate the minimum engineering control requirements to how they contribute to attaining a “state of control”
• Identify the various tests performed during certification of primary and secondary engineering controls
• Apply FDA published citations to determine certification priorities
Facility Engineering Control Certification

- Certifier Qualification
  - NSF Accreditation
    - www.nsf.org
  - CNBT Accreditation
    - http://cetaboardoftesting.org/

- Certification reference material
  - Controlled Environment Testing Association (CETA)
    - www.cetainternational.org
USP Chapter <797>

• “Certification procedures such as those outlined in ‘Certification Guide for Sterile Compounding Facilities’ (CAG-003-2006) shall be performed by a qualified individual no less than every 6 months and whenever the device or room is relocated or altered or major service to the facility is performed”
Facility Objectives

• USP Chapter <797>
  – “Compounding facilities are physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites”

• Objective
  – ISO Classified spaces maintained during operations
    » ISO 7 or 8 rooms
    » ISO 5 PECs
Facility Objectives

• Maintaining ISO classification during operations is a symptom of sound design principles well executed
  – Establish a **State of Control** to reach an objective
    • Engineering controls employed in sterile compounding use **Airflow** through **High Efficiency Particulate Air (HEPA) filters** to create air of appropriate **Cleanliness Classification**.
      • **Airflow**
        • Flow control or Dilution control
        • Segregation
        • Temperature, humidity
      • **Filtration**
        – The **objective** is the **Cleanliness Classification**
Airflow Testing

• ISO Class 5
  – Unidirectional airflow
    • Flow controlled areas are measured in terms of velocity.
    • IEST-RP-CC006.3 section 6.1.2.b

• ISO Class 7, 8
  – Turbulent airflow
    • Dilution control areas are measured in terms of air change rates, volumetric airflow
    • IEST-RP-CC006.3 section 6.1.2.a
Airflow Testing

• Equipment for testing airflow velocity for unidirectional airflow
  – CAG-003
    • Thermal anemometer
    • Multi-Point Array (Velgrid)
Airflow Testing

- Equipment for testing volumetric airflow for turbulent airflow applications - Rooms
  - CAG-003
    - Capture Hood
Airflow Testing

• Non-unidirectional airflow
  – USP <797> objectives
    • Air changes are based on *Supply air* for positive and negative pressure rooms
      – In conflict with traditional balancing paradigms
        » Air exchange rates are typically based on whichever airflow volume is greatest
Airflow Testing

- Acceptance Criteria for turbulent airflow
  - Determined based on facility design
    - Minimum 30 total ACPH for ISO Class 7
    - Establish "state of control" value
      - If initial test indicates significantly more than 30 ACPH, the “state of control point” should be adjusted from 30.
  - 30 ACPH is not adequate for every facility
  - Minimum ACPH must be established for ISO Class 8 areas
    - Suggest 20+ ACPH
Room Segregation

• Equipment for testing room differential pressure
  – Electronic manometer with resolution to at least 0.001” w.c.
    • Will document to nearest 0.01”
    • Inclined manometer or mechanical differential pressure gauge are also listed as acceptable in IEST-RP-CC006.3
  – Ventilation smoke tubes
Room Segregation

• USP <797> for Displacement Airflow
  – “For buffer areas not physically separated from the ante-areas, the principle of displacement airflow shall be employed”
  • Minimum of 40 fpm across the LOD or opening
Room Segregation

• Equipment for testing displacement airflow testing
  – Electric micromanometer with single or multipoint probe (tube array sensor), thermal anemometer, or equivalent
  – Airflow visualization source such as ventilation smoke tubes or other near neutrally buoyant medium
HEPA Filter Integrity Test

- CAG-003-2006 section 2.8
  - All HEPA filters shall be leak tested every certification utilizing an aerosol photometer and an appropriate aerosol challenge
    - A challenge of 10-90 µg/l should be used
    - Reference IEST-RP-CC0034.3
Airflow Smoke Pattern Test

• An airflow smoke pattern test shall be conducted on every PEC and to verify all room segregation relationships are consistent across the entire opening, gap, or crevice.
USP Position

• The airflow in the PEC shall be unidirectional (laminar flow) and because of the particle collection efficiency of the filter, the “first air” at the face of the filter is, for the purposes of aseptic compounding, free from airborne particulate contamination.

• “Proper design and control prevents turbulence and stagnant air in the critical area. In situ air-pattern analysis via smoke studies shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic (working) conditions.”
Relevant Industry Guidelines

• CETA CAG-003-2006
  – “An airflow smoke pattern test should be performed on all unidirectional airflow cleanzones to verify unidirectional airflow”
  – For airflow displacement room segregation testing
    • “The airflow velocity measurements should be supported with a visual smoke pattern analysis”

• FDA Aseptic Processing Guide
  – “In situ air-pattern analysis shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions”
Smoke Pattern Test Objectives

• Primary Engineering Controls
  – At-rest tests should confirm manufacturers and industry expected minimum performance for a unidirectional airflow device
  – Dynamic operating condition tests should confirm that the device works as intended for the operation

• Secondary Engineering Controls
  – Confirm pressure/flow consistent across entire opening from one space to another
Smoke Pattern Testing

Manufacturer/ Industry Procedures
Smoke Pattern Testing

Process integration testing
What is Particle Counting?

• Particle counting is the measurement of particles in the air
  – ISO 14644-1
• It is typically reported in particles per cubic meter (m³)
• **Viable particle counting** - the measurement of particles containing one or more living organisms
• **Non-viable particle counting** - the measurement of all particles without regard to whether they contain living microorganisms
Particle Sampling

- Non-Viable sampling is done with a discrete laser particle counter
Equipment Used in **Particle Sampling**

- Viable sampling is done using one or more of the following samplers: impaction, slit-to-agar, settling plates, etc.
Optional Tests

• Temperature
  – Acceptance
    • Determined by owner
      – USP <797> recommends <20°C (68°F)
      – Most commonly cited comfort zone for the level of gowing worn in sterile compounding is 64-68°F

• Humidity
  – Acceptance
    • Determined by owner
      – USP <797> has no recommendation
      – Most commonly cited range for humidity is 35% RH to 60% RH
FDA Observations

• 2013 Pharmacy Inspections and Related Records
  – http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicREadingRoom/ucm340853.htm
  – 483s (Observations) and Warning Letters
OBSERVATION 3

Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable construction to facilitate cleaning, maintenance, and proper operations.

Specifically, your firm's clean room and anteroom are not designed and built to maintain good aseptic processing operations and do not have adequate air pressure differential and cascade. Also, your firm has not performed smoke studies to verify unidirectional air flow during static and dynamic conditions in laminar flow hoods (identified as ISO 5).

On December 12th, 2013 we observed the ante-room (identified as ISO 8) does not have air supply ducts installed. The anteroom is separated from the clean room (ISO 7) and the mixing room (ISO 8) by strips of plastic hanging in the intervening doorways. Your firm's procedure (SOP #4.330, ver 1.0, eff 9/25/2013) states that a differential pressure of (b) 4 inches of water is expected to exist between these rooms separated only by strips of plastic that do not create a continuous barrier between the rooms.
Your firm’s Cleanroom Certification & Biological Sampling Report (dated August 29, 2013) document provided by a third party certifying contractor shows that air pressure differentials between these rooms are 0.0039 inches of water (clean room to ante-room) and 0.0014 (ante-room to mixing room). The mixing room identified as ISO 8 environment has non-filtered air supply moving down the differential into the ante-room represented in the report referenced above. The ante-room is constructed without an air exhaust vent.

Additionally, there have been no smoke studies performed to evaluate the unidirectional flow of ISO 5 hoods, the clean room, or the ante-room. This includes smoke studies in both static and dynamic conditions.

We observed the clean room and ISO 5 hoods used to [b] [4] and fill products intended to be sterile injectable such as Calcium Edetate (lot #11192013@27) and Glycyrrhizic Acid (lot #11202013@31).
Observation 4: The firm did not review, approve, reject, or comment on whether bacterial and fungal air results from viable air monitoring conducted by an independent company against USP <797> standards is acceptable or not. There is no statement of result conclusion such as passed, failed, meet USP <797>, and not meet USP <797> from the independent certification company. There was no evaluation of the air volume of [redacted] collected in ISO 5 area is representative compared to a bio hood (smaller) with [redacted] of air taken.

Observation 7: A training video using smoke to demonstrate air flow pattern in ISO 5 working areas under a static condition (without production) performed in August of 2012 showed turbulent and upward airflow around the stainless steel working surfaces #2 and #3 (over to the right of the room when viewing from outside) in ISO 5 area. These working surfaces #2 and #3 are used for aseptic filling of sterile drug products. The firm did not take any action to correct the turbulent and upward airflow over working surfaces #2 and #3. The firm has not conducted any dynamic smoke studies to verify the unidirectional airflow and air turbulence within the critical area where sterilized drug products, containers, and closures are exposed to environmental conditions.
OBSERVATION 1

b) On 6/8/13 a 3rd party performed qualification of the Laminar Flow Hoods (LFH) in the cleanroom where sterile products are prepared. A leak was detected in the lower center portion of the HEPA filter in Hood #1. The previous qualification for this hood was performed on 11/1/12, at which time no leak was detected. No investigation was performed by your firm to determine what impact if any this leak would have on product quality. Your firm did not document the hood used for lots that were produced from 11/1/12-6/8/13. A review of the log for the [redacted] [b]4[b] #4 from 3/27/13-6/7/13, which is used for some products made in Hood #1, there were at least [redacted] [b]4[b] lots made in Hood #1 during that time period.

This is a repeat observation from the 3/18-22/13 inspection.

d) Your firm is not performing smoke studies in the ISO 5 Laminar Flow Hoods under dynamic conditions. These Laminar Flow Hoods are where your firm performs aseptic processing of sterile drug products.
OBSERVATION 1

iv. Non-viable particulate (NVP) monitoring is not performed during routine production. It is only performed approximately every \( (b) \,(4) \) during cleanroom HEPA certification.

C. Adequate documentation was not provided to support that air pattern analyses (smoke studies) of the ISO 5 laminar flow hoods are performed under dynamic conditions representative of aseptic processing operations to ensure uniform air flow over exposed product and materials. An air pattern smoke test is performed during the semi-annual HEPA certification of the ISO 5 laminar flow hoods. No video of this is maintained. Air pattern analysis of the ISO 7 buffer room, where the laminar flow hoods are located, has not been performed.

OBSERVATION 2

A. The HEPA filter grate cover for ISO 5 laminar flow hood #1 was observed with what appeared to be residues and rust-like spots. This grate cover is not cleaned during regular cleaning of the laminar flow hood, and no cleaning or maintenance frequency is specified for this grate.

B. Filter Integrity (leak) Testing has not been performed for the HEPA filters supplying the ISO 7 cleanroom (prep, ante, and buffer rooms) which were installed in 01/2013. Only non-viable particulate monitoring of these HEPA filters for the ISO 7 rooms is performed every \( (b) \,(4) \).

C. The pressure differential between the ISO 5 laminar flow hoods and the ISO 7 cleanroom is not monitored continuously. Hood #2 has no pressure gauge for routine monitoring, and hood #1 is monitored \( (b) \,(4) \).